Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603 838 individuals

Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603 838 individuals

Mika Kivimäki, Markus Jokela, Solja T Nyberg, Archana Singh-Manoux, Eleonor I Fransson, Lars Alfredsson, Jakob B Bjorner, Marianne Borritz, Hermann Burr, Annalisa Casini, Els Clays, Dirk De Bacquer, Nico Dragano, Raimund Erbel, Goedele A Geuskens, Mark Hamer, Wendela E Hooftman, Irene L Houtman, Karl-Heinz Jöckel, France Kittel, Anders Knutsson, Markku Koskenvuo, Thorsten Lunau, Ida E H Madsen, Martin L Nielsen, Maria Nordin, Tuula Oksanen, Jan H Pejtersen, Jaana Pentti, Reiner Rugulies, Paula Salo, Martin J Shipley, Johannes Siegrist, Andrew Steptoe, Sakari B Suominen, Töres Theorell, Jussi Vahtera, Peter J M Westerholm, Hugo Westerlund, Dermot O'Reilly, Meena Kumari, G David Batty, Jane E Ferrie, Marianna Virtanen, for the IPD-Work Consortium

Summary

Background Long working hours might increase the risk of cardiovascular disease, but prospective evidence is scarce, imprecise, and mostly limited to coronary heart disease. We aimed to assess long working hours as a risk factor for incident coronary heart disease and stroke.

Methods We identified published studies through a systematic review of PubMed and Embase from inception to Aug 20, 2014. We obtained unpublished data for 20 cohort studies from the Individual-Participant-Data Meta-analysis in Working Populations (IPD-Work) Consortium and open-access data archives. We used cumulative random-effects meta-analysis to combine effect estimates from published and unpublished data.

Findings We included 25 studies from 24 cohorts in Europe, the USA, and Australia. The meta-analysis of coronary heart disease comprised data for 603 838 men and women who were free from coronary heart disease at baseline; the meta-analysis of stroke comprised data for 528 908 men and women who were free from stroke at baseline. Follow-up for coronary heart disease was 5·1 million person-years (mean 8·5 years), in which 4768 events were recorded, and for stroke was 3·8 million person-years (mean 7·2 years), in which 1722 events were recorded. In cumulative meta-analysis adjusted for age, sex, and socioeconomic status, compared with standard hours (35–40 h per week), working long hours (≥55 h per week) was associated with an increase in risk of incident coronary heart disease (relative risk [RR] 1·13, 95% CI 1·02–1·26; p=0·02) and incident stroke (1·33, 1·11–1·61; p=0·002). The excess risk of stroke remained unchanged in analyses that addressed reverse causation, multivariable adjustments for other risk factors, and different methods of stroke ascertainment (range of RR estimates 1·30–1·42). We recorded a dose–response association for stroke, with RR estimates of 1·10 (95% CI 0·94–1·28; p=0·24) for 41–48 working hours, 1·27 (1·03–1·56; p=0·03) for 49–54 working hours, and 1·33 (1·11–1·61; p=0·002) for 55 working hours or more per week compared with standard working hours (p_{trend}<0·0001).

Interpretation Employees who work long hours have a higher risk of stroke than those working standard hours; the association with coronary heart disease is weaker. These findings suggest that more attention should be paid to the management of vascular risk factors in individuals who work long hours.

Funding Medical Research Council, Economic and Social Research Council, European Union New and Emerging Risks in Occupational Safety and Health research programme, Finnish Work Environment Fund, Swedish Research Council for Working Life and Social Research, German Social Accident Insurance, Danish National Research Centre for the Working Environment, Academy of Finland, Ministry of Social Affairs and Employment (Netherlands), US National Institutes of Health, British Heart Foundation.

Introduction

Long working hours have been implicated in the cause of cardiovascular disease.[1–4] In two meta-analyses of published cohort studies,[1,2] the risk of coronary heart disease was raised in employees working long hours compared with those working standard hours.[1,2] The relative risk was about 1·4, which, if substantiated, is substantial, because long working hours are fairly common.[5] However, several limitations in these studies could have biased the estimates.

First, publication bias (the increased likelihood that studies with significant findings will be published) might have distorted the evidence. Second, reverse causation might have changed effect estimates if employees with advanced underlying cardiovascular disease reduced their working hours in the years before the cardiovascular

Lancet 2015; 386: 1739–46

Published **Online** August 20, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60295-1

See **Comment** page 1710

Department of Epidemiology and Public Health, University College London, London, UK (Prof M Kivimäki PhD, A Singh-Manoux PhD, M Hamer PhD, M J Shipley MSc, Prof A Steptoe DSc, Prof M Kumari PhD, G D Batty DSc, J E Ferrie PhD); **Department of Public Health** (Prof M Koskenvuo MD), **Faculty of Medicine** (Prof M Kivimäki), **and Institute of Behavioral Sciences** (M Jokela PhD), **University of Helsinki, Helsinki, Finland; Finnish Institute of Occupational Health, Helsinki, Tampere and Turku, Finland** (S T Nyberg MSc, T Oksanen MD, J Pentti MSc, Prof P Salo PhD, Prof J Vahtera MD, Prof M Virtanen PhD); **Inserm U1018, Centre for Research in Epidemiology and Population Health, Villejuif, France** (A Singh-Manoux); **Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden** (E I Fransson PhD, Prof L Alfredsson PhD); **School of Health Sciences, Jönköping University, Jönköping, Sweden** (E I Fransson); **Stress Research Institute, Stockholm University, Stockholm, Sweden** (E I Fransson, M Nordin PhD, Prof T Theorell MD, Prof H Westerlund PhD); **Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden** (Prof L Alfredsson); **National Research Centre for the Working Environment,**

Copenhagen, Denmark (Prof J B Bjorner MD, I E H Madsen PhD, Prof R Rugulies PhD); **Department of Occupational Medicine, Koege Hospital, Copenhagen, Denmark** (M Borritz MD); **Federal Institute for Occupational Safety and Health (BAuA), Berlin, Germany** (H Burr PhD); **School of Public Health, Université libre de Bruxelles (ULB), Brussels, Belgium** (A Casini PhD, Prof F Kittel PhD); **Department of Public Health, Ghent University, Ghent, Belgium** (E Clays PhD, Prof D De Bacquer PhD); **Institute for Medical Sociology, Medical Faculty, University of Düsseldorf, Düsseldorf, Germany** (Prof N Dragano PhD, T Lunau MSc, Prof J Siegrist PhD); **Department of Cardiology, West-German Heart Center Essen, University Duisburg-Essen, Essen, Germany** (Prof R Erbel MD); **TNO, Hoofddorp, Netherlands** (G A Geuskens PhD, W E Hooftman PhD, I L Houtman PhD); **Institute for Medical Informatics, Biometry, and Epidemiology, Faculty of Medicine, University Duisburg-Essen, Essen, Germany** (Prof K-H Jöckel); **Department of Health Sciences, Mid Sweden University, Sundsvall, Sweden** (Prof A Knutsson MD); **Unit of Social Medicine, Frederiksberg University Hospital, Copenhagen, Denmark** (M L Nielsen MD); **Department of Psychology, Umeå University, Umeå, Sweden** (M Nordin); **The Danish National Centre for Social Research, Copenhagen, Denmark** (J H Pejtersen PhD); **Department of Public Health and Department of Psychology, University of Copenhagen, Copenhagen, Denmark** (Prof R Rugulies); **Department of Psychology** (Prof P Salo) **and Department of Public Health** (Prof S B Suominen MD, Prof J Vahtera), **University of Turku, Turku, Finland; Folkhälsan Research Center, Helsinki, Finland** (Prof S B Suominen); **University of Skövde, Skövde, Sweden** (Prof S B Suominen); **Turku University Hospital, Turku, Finland** (Prof J Vahtera); **Occupational and Environmental Medicine, Uppsala University, Uppsala,**

event.[3] Third, the association might be confounded; working long hours is more common in high socioeconomic status (SES) occupations,[6] but the incidence of cardiovascular diseases is higher in low SES occupations.[7] Fourth, few studies have examined long working hours as a risk factor for stroke, a major cardiovascular endpoint,[8,9] although stress and extensive sitting, both of which are associated with long working hours, could increase the risk of stroke.[10,11]

We did this meta-analysis of prospective cohort studies assessing long working hours and cardiovascular disease to overcome these limitations. We supplement published studies identified by systematic review with unpublished individual-participant data to examine the effect of publication bias and increase the precision of the estimates. Additionally, we address bias due to reverse causation by excluding disease events that took place in the first years of follow-up, control for confounding by stratifying analyses by SES, and examine associations with incident stroke and coronary heart disease.

Methods

Search strategy and selection criteria

In accordance with the PRISMA guidelines,[12] we identified published studies through a systematic review of PubMed and Embase from inception to Aug 20, 2014, with the following search terms without restrictions: ("work hours", "working hours", "overtime work") and ("coronary heart disease", "ischemic heart disease", "acute myocardial infarction", "angina pectoris", "chest pain", "stroke", "cerebrovascular", "cerebrovascular disease"). We also scrutinised the reference lists of all relevant major reviews,[1,2,13–15] and those of the eligible publications, and did a cited reference search using the Institute of Scientific Information Web of Science.

After exclusion of duplicate studies, two investigators (MKi and MV) independently reviewed titles and abstracts of the remaining articles to establish their eligibility on the basis of predefined inclusion criteria. We included studies that were published in English; had a prospective cohort study design with individual level exposure and outcome data; examined the effect of working hours; reported incident coronary heart disease or stroke as an outcome; and reported either estimates of relative risk (RR), odds ratios (ORs), or hazard ratios (HRs) with 95% CIs, or provided sufficient results to calculate these estimates.

Data extraction

We extracted the following information from each eligible article: name of the first author, start of the follow-up for coronary heart disease or stroke (year), study location (country), number of participants, number of coronary heart disease or stroke events, mean follow-up time, mean age of participants, proportion of women, method of coronary heart disease or stroke ascertainment, and covariates included in the adjusted models.

Unpublished individual-participant data

We supplemented data from the published studies with unpublished individual-level data from 13 European prospective cohort studies participating in the Individual-Participant-Data Meta-analysis in Working Populations (IPD-Work) Consortium (appendix).[16–29]

We located additional individual-level data by searching the Inter-University Consortium for Political and Social Research and the UK Data Service to identify eligible large-scale cohort studies for which data were publicly available. Seven cohort studies were identified (appendix).[30–36] All the studies with unpublished data

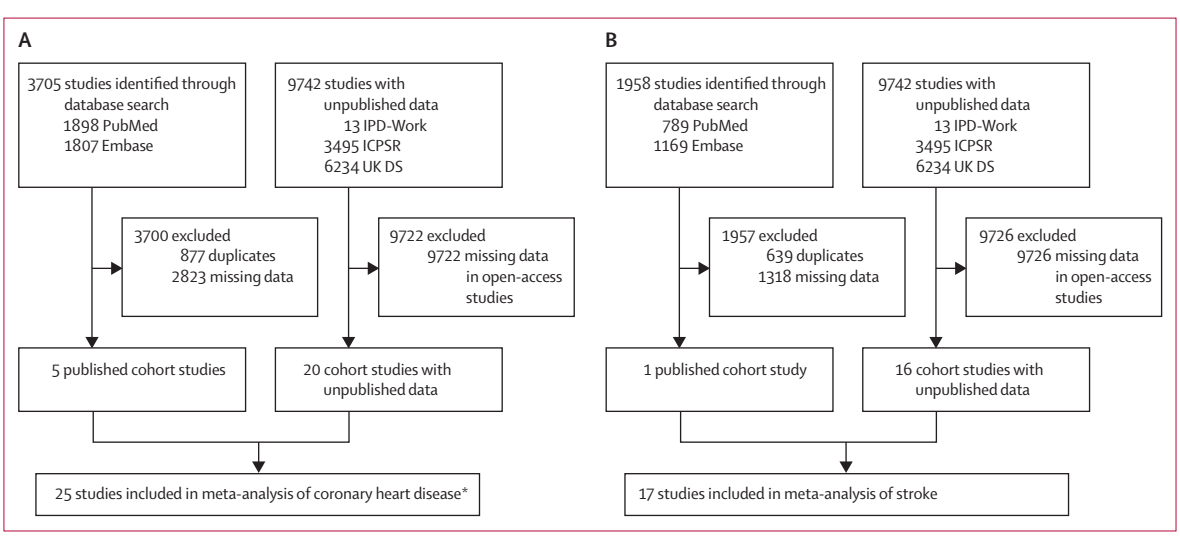

Figure 1: **Study selection**
(A) Long working hours and coronary heart disease. (B) Long working hours and stroke. *In one study published data[41] were used in the main analysis, but unpublished data from the IPD-Work Consortium[17] were used in subgroup and sensitivity analyses. IPD-Work=Individual-Participant-Data Meta-analysis in Working Populations Consortium. ICPSR=Inter-University Consortium for Political and Social Research. UK DS=UK Data Service.

were approved by the relevant local or national ethics committee and all participants gave informed consent to participate.

Harmonised covariates, including potential confounding and mediating factors, were age, sex, SES,[16] smoking,[37] body-mass index (BMI),[38] physical activity,[39] and alcohol consumption.[40] Additional covariates not available for all the studies were total cholesterol or hypercholesterolaemia, systolic blood pressure or hypertension, and diabetes.[41]

Quality assessment

To assess the quality of included studies, we used the Cochrane Risk of Bias Tool for cohort studies.[42] We analysed selection of exposed and non-exposed groups, assessment of exposure, exclusion of the outcome of interest at study baseline, adjustment for confounding variables, assessment of confounding variables, assessment of outcome, and adequacy of the follow-up. The quality of the study was regarded as high if all domains were assessed favourably.

Statistical analysis

Because the proportional hazards assumption was not violated in the unpublished IPD-Work data (all p>0·20), we used Cox proportional hazards models to generate HRs and 95% CIs for the association between working hours and coronary heart disease or stroke in each of the IPD-Work studies. In the open-access studies, incident coronary heart disease and stroke events were self-reported and had no precise date of event. For these studies, we used logistic regression to calculate study specific ORs and 95% CIs for the association between working hours and coronary heart disease or stroke.

We used meta-analysis to combine the results from the analyses of the unpublished data and the estimates from the published studies reported as HRs or ORs. Because disease incidence was low in the cohort studies, we regarded ORs as close approximations of RR and combined them with HRs, resulting in a common estimate of RR.[43] In accordance with the Meta-Analysis of Observational Studies guidelines,[44] we used all available data in the main analysis and did a sensitivity analysis including only high-quality studies according to the assessment of bias.

We analysed associations of long working hours with incident coronary heart disease and stroke separately. The basic model included age, sex, and SES as covariates. For the unpublished individual-participant data, multivariable adjusted models were additionally adjusted for smoking, alcohol consumption, BMI and physical activity, total cholesterol or hypercholesterolaemia, systolic blood pressure or hypertension, and diabetes; the number of covariates depended on the availability of data. For published studies, we used the most comprehensively adjusted estimates in multivariable adjusted models.

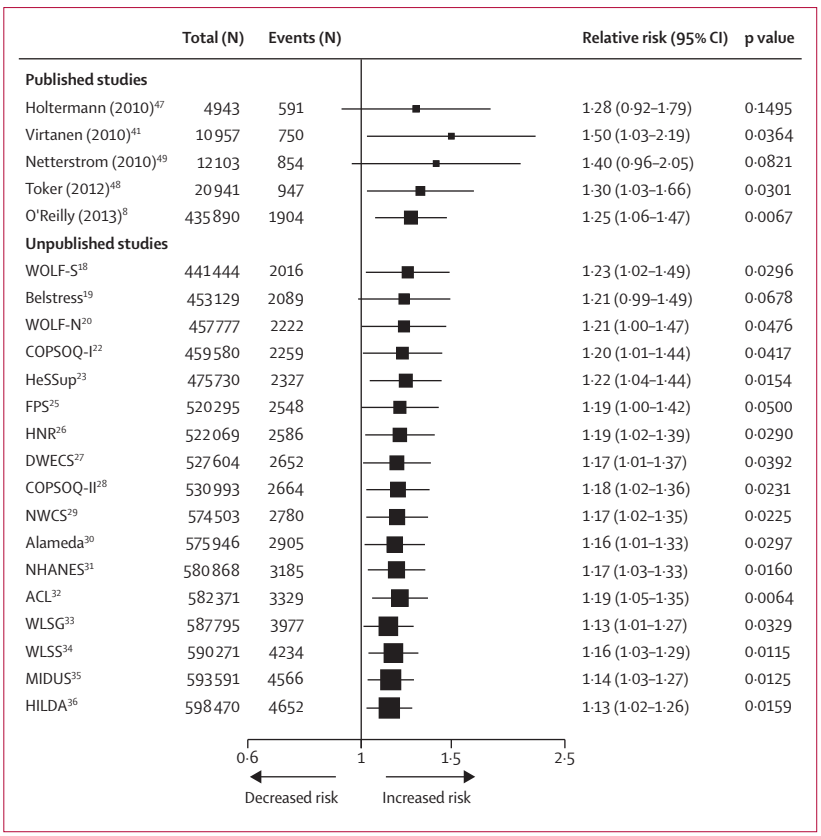

Figure 2: **Cumulative meta-analysis of published and unpublished data of the association between long working hours and incident coronary heart disease**
Estimates adjusted for age, sex, and socioeconomic status.

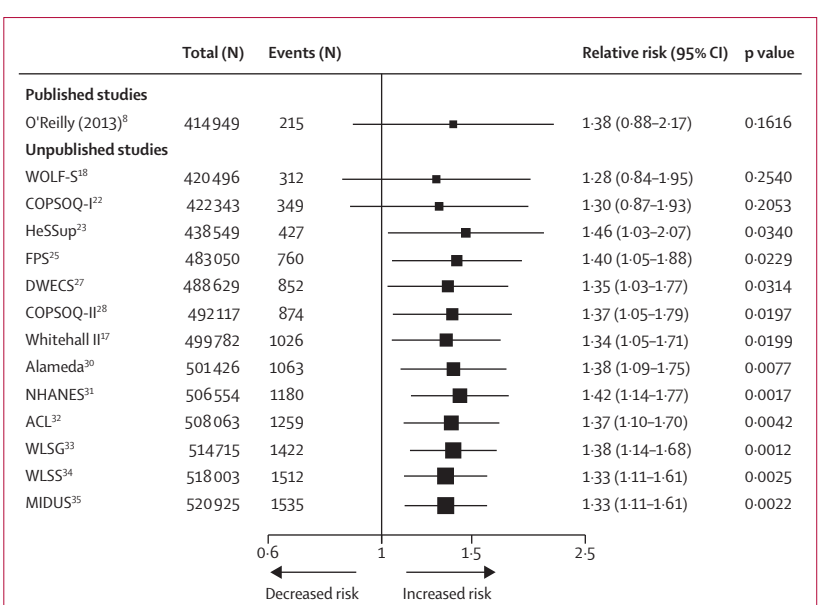

Figure 3: **Cumulative meta-analysis of published and unpublished data of the association between long working hours and incident stroke**
Estimates adjusted for age, sex, and socioeconomic status.

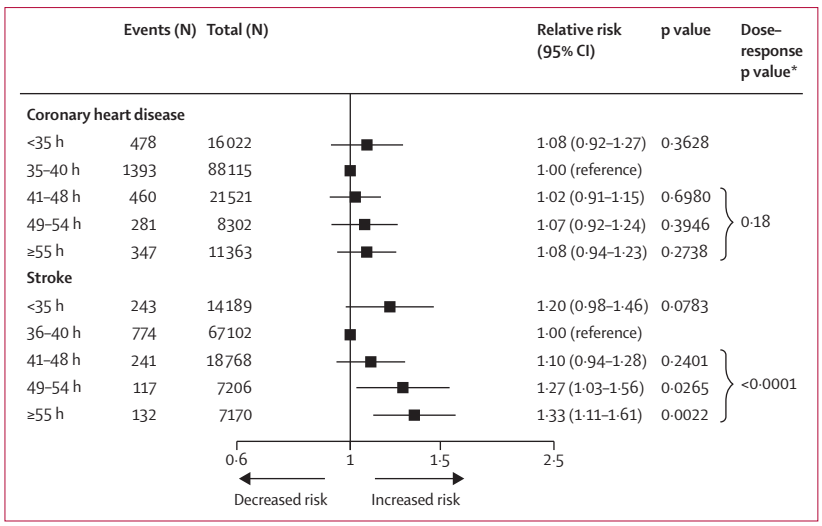

Figure 4: **Association of categories of weekly working hours with incident coronary heart disease and stroke**
Estimates adjusted for age, sex, and socioeconomic status. *For trend from standard to long working hours.

Sweden (Prof P J M Westerholm MD); **Centre for Public Health, Queen's University Belfast, Belfast, UK** (D O'Reilly PhD); **Institute for Social and Economic Research, University of Essex, Colchester, UK** (Prof M Kumari); **Centre for Cognitive Ageing and Cognitive Epidemiology and Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK** (G D Batty); **and School of Community and Social Medicine, University of Bristol, Bristol, UK** (J E Ferrie)

Correspondence to: Prof Mika Kivimäki, Department of Epidemiology and Public Health, University College London WC1E 6BT, UK **m.kivimaki@ucl.ac.uk**

See Online for appendix

For the **Inter-University Consortium for Political and Social Research** see http://www.icpsr.umich.edu/icpsrweb/ICPSR/

For the **UK Data Service** see http://ukdataservice.ac.uk/

We examined heterogeneity of the study-specific estimates with the I^2 statistic (higher values denote greater heterogeneity) and present the summary estimates of the random-effects analysis.[45] To describe the development of evidence over time, we did a cumulative meta-analysis of the association of working hours with coronary heart disease and stroke, based on date of publication and, for the IPD-Work and open-access unpublished data, year of baseline examination.[46] We estimated dose–response associations with generalised least-squares analysis of trend based on numbers of events and participants, effect estimates, and standard errors for the working hours categories (35–40 h, 41–48 h, 49–54 h, and ≥55 h per week).

We examined reverse causation by left-censoring—ie, exclusion from the analysis of coronary heart disease and stroke events that took place in the first 3 years of follow-up.[6,16] Only studies in which definite event times were known were used in this analysis. Prespecified subgroup analyses were done by sex, age group (<50 *vs* ≥50 years), SES (high, intermediate, low), region (Europe [including Israel] *vs* USA), method of outcome ascertainment (medical records *vs* self-report), and publication status (published *vs* unpublished), and assessed group differences with meta-regression. We examined publication bias in published studies with funnel plots.

We did statistical analyses with SAS (version 9.2) or Stata (MP version 11.2) to analyse study specific data, with the exception of data from the Netherlands Working Conditions Survey (NWCS)[29] for which we used SPSS (version 19). We used Stata (MP version 11.2) to compute the meta-analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MKi, STN, IEHM, and WEH had full access to the IPD-Work consortium data and MJ had full access to the open-access datasets. MKi had final responsibility for the decision to submit for publication.

Results

Figure 1 shows a flow diagram for the study selection process. We identified 3705 studies of working hours and coronary heart disease and 1958 studies of working hours and stroke (figure 1). Six studies were eligible for inclusion: five about coronary heart disease[8,41,47–49] and one about stroke (figure 1).[8] We did not include two studies[50–52] that were included in previous meta-analyses[1,2] because they did not meet the inclusion criteria (the outcome was a cerebro–cardiovascular composite rather than either coronary heart disease or stroke). In combination, the published and unpublished data included in this meta-analysis comprised 25 studies from the USA,[30–35] Australia,[36] Finland,[23,25] Denmark,[21,22,24,27,28,47,49] Sweden,[18,20] the Netherlands,[29] Belgium,[19] Germany,[26] the UK,[17,41] Northern Ireland,[8] and Israel.[48] The definition of long working hours varied across published studies from 45 h or more[47] to 55 h or more per week.[8,41] In the studies with unpublished data,[17–36] 55 h or more per week are defined as long working hours and the reference category is 35–40 h. The appendix details characteristics of the study populations and quality assessment of the studies included. 17 (68%) of the 25 studies were assessed as being of high quality.[17–29,41,47,48,49]

603 838 men and women free from coronary heart disease at baseline contributed to the analysis of long working hours and incident coronary heart disease. 4768 of these individuals had an event during the mean follow-up of 8·5 years. Four of the five published studies and all the IPD-Work studies had a uniform definition of incident coronary heart disease, with non-fatal myocardial infarction (I21–I22 in International Classification of Diseases [ICD]-10; 410 in ICD-9; or in line with WHO MONICA definitions)[53] or coronary death (I21–I25 in ICD-10; 410–414 in ICD-9) recorded as the main cause of hospital admission or death.[17–29,41,47–49] In one published study, the outcome was fatal ischaemic heart disease from a national mortality register.[8] In studies from the open-access archives, incident coronary heart disease was assessed by self-report.

Figure 2 shows results of the cumulative meta-analysis adjusted for age, sex, and socioeconomic status. We excluded three IPD-Work studies from this analysis: Whitehall II[41] to avoid overlap with published data, and IPAW[21] and PUMA[24] because of no events in the exposure group. Working long hours was associated with a modest overall increase in risk of incident coronary heart disease compared with working standard hours (RR 1·13, 95% CI 1·02–1·26; p=0·02; figure 2). There was no significant heterogeneity in the study-specific estimates (I^2=0%, p=0·49; appendix).

528 908 men and women free from stroke at baseline contributed to the analysis of long working hours and incident stroke. 1722 of these individuals had an event during mean follow-up of 7·2 years. The only published study available assessed fatal, but not non-fatal, stroke.[8] Incident stroke in the IPD-Work studies was defined with hospital and mortality records (I60, I61, I63, I64 in ICD-10; 430, 431, 433, 434, 436 in ICD-9). Incident stroke was based on self-reported data in the open-access datasets.

We excluded three IPD-Work studies from the cumulative meta-analysis of incident stroke (WOLF-N,[20] IPAW[21], and PUMA[24]) because of no events in the exposure group. Working long hours was associated with an increased risk of incident stroke (RR 1·33, 95% CI 1·11–1·61; p=0·002; figure 3). Again, there was no significant heterogeneity in the study-specific estimates (I^2=0%, p=0·67; appendix).

None of the published studies reported numbers of participants and events and RR for all categories of working hours. Thus, only IPD-Work and the open-access studies (20 for coronary heart disease[17–36] and 16 for stroke[17,18,20–25,27,28,30–35]) contributed to the dose–response analyses. No linear trend from standard to long working hours was shown for coronary heart disease; by contrast, we recorded a dose–response association for stroke (figure 4), for which the RR per one category increase in working hours was 1·11 (95% CI 1·05–1·17).

We recorded no evidence of significant bias arising from reverse causation, confounding, outcome ascertainment, publication status, geographical region, loss to follow-up, or study quality in the associations of long working hours with coronary heart disease and stroke (figure 5, appendix). Any subgroup differences were small with one exception: an analysis limited to high-quality studies showed an SES-dependent association between long working hours and coronary heart disease, with an RR of 2·18 (95% CI 1·25–3·81; p=0·006) in the low SES group, 1·22 (0·77–1·95; p=0·40) in the intermediate SES group, and 0·87 (0·55–1·38; p=0·56) in the high SES group (p=0·001 for difference between groups; appendix).

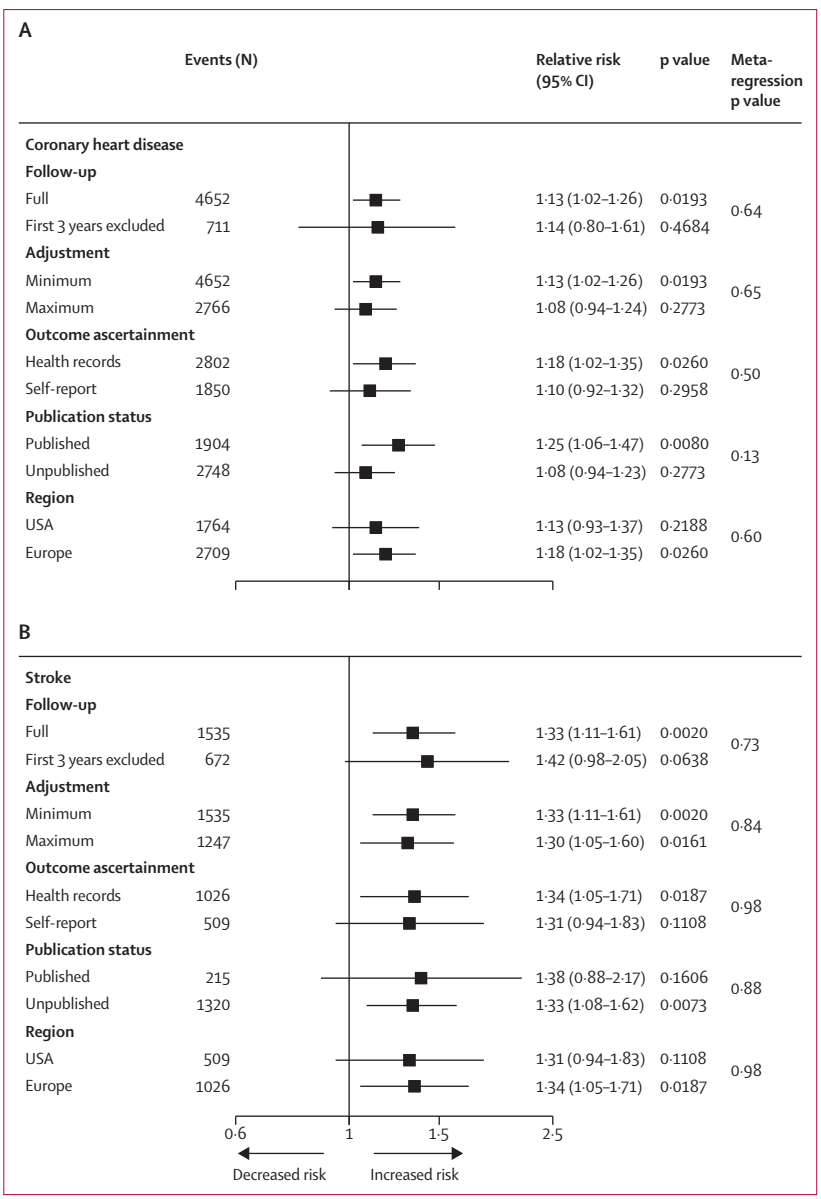

Figure 5: **Association of long working hours with incident coronary heart disease and stroke in relation to study follow-up, adjustments, outcome ascertainment, publication status, and region**
(A) Coronary heart disease. (B) Stroke. Estimates adjusted, when appropriate, for age, sex, and socioeconomic status.

Discussion

Our findings show that individuals who work 55 h or more per week have a 1·3-times higher risk of incident stroke than those working standard hours. There was no evidence of between-study heterogeneity, reverse causation bias, or confounding. Furthermore, the association did not vary between men and women or by geographical region, and was independent of the method of stroke ascertainment, suggesting that the finding is robust. Long working hours were also associated with incident coronary heart disease, but this association was weaker than that for stroke.

Combining estimates from published studies and unpublished data allowed us to examine the status of long working hours as a risk factor for coronary heart disease and stroke with greater precision and a more comprehensive evidence base than has previously been possible. Our findings are consistent with two previous meta-analyses[1,2] of long working hours and coronary heart disease reviewing prospective data from less than 15 000 participants—a substantially smaller evidence base than that in the present meta-analysis. Socioeconomic differences in the association between long working hours and coronary heart disease have been reported for mortality from ischaemic heart disease in Northern Ireland.[8] Our meta-analysis of high-quality cohort studies confirms a stronger association for fatal

and non-fatal incident coronary heart disease in individuals with low SES occupations than in those with high SES occupations.

We are not aware of previous prospective cohort studies of the association between long working hours and incident stroke, although this association is biologically plausible. Sudden death from overwork is often caused by stroke and is believed to result from a repetitive triggering of the stress response.[4,54] Behavioural mechanisms, such as physical inactivity, might also link long working hours and stroke; a hypothesis supported by evidence of an increased risk of incident stroke in individuals who sit for long periods at work.[11] Physical inactivity can increase the risk of stroke through various biological mechanisms,[55–58] and heavy alcohol consumption—a risk factor for all types of stroke[59–61]—might be a contributing factor because employees working long hours seem to be slightly more prone to risky drinking than are those who work standard hours.[62] Some, albeit inconsistent, evidence suggests that individuals who work long hours are more likely to ignore symptoms of disease and have greater prehospital delays in relation to acute cardiovascular events than do those who work standard hours.[63]

Our meta-analysis has some limitations. A large proportion of the unpublished individual-participant data was from the IPD-Work Consortium, which is based on a convenience sample potentially contributing to availability bias. Exposure to long working hours was based on self-report and was measured only once. Because the tendency to work long hours is not necessarily stable over time, further research on prolonged exposure to long working hours, preferably with objective measures, is needed to establish whether our findings are underestimated because of misclassification of the exposure. In two studies,[30,36] high loss to follow-up could also have contributed to an underestimation of associations, although this bias seemed to be small or absent in the total data. We had harmonised data for multivariable adjustments for age, sex, SES, smoking, BMI, physical activity, and alcohol consumption, but not for salt intake and blood-based risk factors. Ascertainment of coronary heart disease and stroke varied, ranging from medical records of brain imaging and autopsy to repeated self-report questionnaires; therefore, some outcome misclassification is possible. However, the absence of heterogeneity in the study-specific estimates, and the uniform findings in the analyses stratified by method of ascertainment, suggest that this misclassification is not a major source of bias.

In conclusion, our meta-analysis shows that employees who work long hours have a higher risk of stroke than those working standard hours. However, the evidence for coronary heart disease is less persuasive. Our findings suggest that more attention should be paid to the management of vascular risk factors in individuals who work long hours.

Declaration of interests

We declare no competing interests.

Contributors

All authors designed the study, generated hypotheses, interpreted the data, and wrote and critically reviewed the report. MKi wrote the first draft of the report. MKi and MV did the literature search. MJ and STN analysed the data. MJ, STN, and MKi had full access to anonymised individual-participant data from all constituent studies, with the exception of data from NWCS, COPSOQ-I, COPSOQ-II, DWECS, IPAW, and PUMA. WEH had full access to NWCS data and IEHM had full access to the individual-participant data from COPSOQ-I, COPSOQ-II, DWECS, IPAW, and PUMA.

Acknowledgments

The IPD-Work Consortium was funded by the European Union New and Emerging Risks in Occupational Safety and Health research programme, the Finnish Work Environment Fund, the Swedish Research Council for Working Life and Social Research, the German Social Accident Insurance (the AeKo-Project), Danish National Research Centre for the Working Environment, the Academy of Finland, the BUPA Foundation (grant 22094477), and the Ministry of Social Affairs and Employment, the Netherlands. MKi is supported by the Medical Research Council (grant number K013351), the UK Economic and Social Research Council, and the US National Institutes of Health (R01HL036310; R01AG034454). AS is supported by the British Heart Foundation.

References

1 Virtanen M, Heikkilä K, Jokela M, et al. Long working hours and coronary heart disease: a systematic review and meta-analysis. *Am J Epidemiol* 2012; **176:** 586–96.

2 Kang MY, Park H, Seo JC, et al. Long working hours and cardiovascular disease: a meta-analysis of epidemiologic studies. *J Occup Environ Med* 2012; **54:** 532–37.

3 Sokejima S, Kagamimori S. Working hours as a risk factor for acute myocardial infarction in Japan: case-control study. *BMJ* 1998; **317:** 775–80.

4 Steptoe A, Kivimäki M. Stress and cardiovascular disease. *Nat Rev Cardiol* 2012; **9:** 360–70.

5 OECD. Recent labour market developments and prospects. Special focus on: clocking in (and out): several facets of working time. Paris: OECD, 2004.

6 Kivimäki M, Virtanen M, Kawachi I, et al. Long working hours, socioeconomic status and the risk of incident type 2 diabetes: a meta-analysis of published and unpublished data from 222 120 individuals. *Lancet Diabetes Endocrinol* 2015; **3:** 27–34.

7 CSDH. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva: World Health Organization, 2008.

8 O'Reilly D, Rosato M. Worked to death? A census-based longitudinal study of the relationship between the numbers of hours spent working and mortality risk. *Int J Epidemiol* 2013; **42:** 1820–30.

9 Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380:** 2224–60.

10 Fransson EI, Nyberg ST, Heikkilä K, et al. Job strain and the risk of stroke: an individual-participant data meta-analysis. *Stroke* 2015; **46:** 557–59.

11 Kumar A, Prasad M, Kathuria P. Sitting occupations are an independent risk factor for Ischemic stroke in North Indian population. *Int J Neurosci* 2014; **124:** 748–54.

12 Moher D, Liberati A, Tetzlaff J, Altman DG, and the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6:** e1000097.

13 van der Hulst M. Long workhours and health. *Scand J Work Environ Health* 2003; **29:** 171–88.

14 Sparks K, Cooper C, Fried Y, Shirom A. The effects of hours of work on health: a meta-analytic review. *J Occup Organ Psychol* 1997; **70:** 391–408.

15 Bannai A, Tamakoshi A. The association between long working hours and health: a systematic review of epidemiological evidence. *Scand J Work Environ Health* 2014; **40:** 5–18.

16 Kivimäki M, Nyberg ST, Batty GD, et al, and the IPD-Work Consortium. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet* 2012; **380:** 1491–97.

17 Marmot MG, Smith GD, Stansfeld S, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet* 1991; **337:** 1387–93.

18 Peter R, Alfredsson L, Hammar N, Siegrist J, Theorell T, Westerholm P. High effort, low reward, and cardiovascular risk factors in employed Swedish men and women: baseline results from the WOLF Study. *J Epidemiol Community Health* 1998; **52:** 540–47.

19 De Bacquer D, Pelfrene E, Clays E, et al. Perceived job stress and incidence of coronary events: 3-year follow-up of the Belgian Job Stress Project cohort. *Am J Epidemiol* 2005; **161:** 434–41.

20 Alfredsson L, Hammar N, Fransson E, et al. Job strain and major risk factors for coronary heart disease among employed males and females in a Swedish study on work, lipids and fibrinogen. *Scand J Work Environ Health* 2002; **28:** 238–48.

21 Nielsen M, Kristensen T, Smith-Hansen L. The Intervention Project on Absence and Well-being (IPAW): design and results from the baseline of a 5-year study. *Work Stress* 2002; **16:** 191–206.

22 Kristensen TS, Hannerz H, Høgh A, Borg V. The Copenhagen Psychosocial Questionnaire—a tool for the assessment and improvement of the psychosocial work environment. *Scand J Work Environ Health* 2005; **31:** 438–49.

23 Korkeila K, Suominen S, Ahvenainen J, et al. Non-response and related factors in a nation-wide health survey. *Eur J Epidemiol* 2001; **17:** 991–99.

24 Borritz M, Rugulies R, Bjorner JB, Villadsen E, Mikkelsen OA, Kristensen TS. Burnout among employees in human service work: design and baseline findings of the PUMA study. *Scand J Public Health* 2006; **34:** 49–58.

25 Kivimäki M, Lawlor DA, Davey Smith G, et al. Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart disease: the Finnish Public Sector study. *Am J Public Health* 2007; **97:** 874–79.

26 Stang A, Moebus S, Dragano N, et al, and the Heinz Nixdorf Recall Study Investigation Group. Baseline recruitment and analyses of nonresponse of the Heinz Nixdorf Recall Study: identifiability of phone numbers as the major determinant of response. *Eur J Epidemiol* 2005; **20:** 489–96.

27 Feveile H, Olsen O, Burr H, Bach E. Danish Work Enviornment Cohort Study 2005: from idea to sampling design. *Stat Transit* 2007; **8:** 441–58.

28 Pejtersen JH, Kristensen TS, Borg V, Bjorner JB. The second version of the Copenhagen Psychosocial Questionnaire. *Scand J Public Health* 2010; **38** (suppl)**:** 8–24.

29 van Hooff M, van den Bossche SNJ, Smulders PGW. The Netherlands working condition survey. Highlights 2003–2006. 2008. http://wwwmzesuni-mannheimde/projekte/mikrodaten/wp_pdf/wp_30_NL-ropdf (accessed Aug 18, 2014).

30 Berkman L, Breslow L. Health and ways of living: the Alameda County Study. New York, NY: Oxford University Press, 1983.

31 Madans JH, Cox CS, Kleinman JC, et al. 10 years after NHANES I: mortality experience at initial followup, 1982–84. *Public Health Rep* 1986; **101:** 474–81.

32 House JS, Lantz PM, Herd P. Continuity and change in the social stratification of aging and health over the life course: evidence from a nationally representative longitudinal study from 1986 to 2001/2002 (Americans' Changing Lives Study). *J Gerontol B Psychol Sci Soc Sci* 2005; **60:** 15–26.

33 Sewell WH, Houser RM. Education, occupation, and earnings: achievement in the early career. New York, 1975.

34 Hauser RM, Sewell WH. Birth order and educational attainment in full sibships. *Am Educ Res J* 1985; **22:** 1–23.

35 Brim OG, Ryff CD. How healthy are we? A national study of well-being at mid-life. Chicago, IL: The University of Chicago Press, 2004.

36 Butterworth P, Crosier T. The validity of the SF-36 in an Australian National Household Survey: demonstrating the applicability of the Household Income and Labour Dynamics in Australia (HILDA) Survey to examination of health inequalities. *BMC Public Health* 2004; **4:** 44.

37 Heikkilä K, Nyberg ST, Fransson EI, et al, and the IPD-Work Consortium. Job strain and tobacco smoking: an individual-participant data meta-analysis of 166 130 adults in 15 European studies. *PLoS One* 2012; **7:** e35463.

38 Nyberg ST, Heikkilä K, Fransson EI, et al, and the IPD-Work Consortium. Job strain in relation to body mass index: pooled analysis of 160 000 adults from 13 cohort studies. *J Intern Med* 2012; **272:** 65–73.

39 Fransson EI, Heikkilä K, Nyberg ST, et al. Job strain as a risk factor for leisure-time physical inactivity: an individual-participant meta-analysis of up to 170 000 men and women: the IPD-Work Consortium. *Am J Epidemiol* 2012; **176:** 1078–89.

40 Heikkilä K, Nyberg ST, Fransson EI, et al, and the IPD-Work Consortium. Job strain and alcohol intake: a collaborative meta-analysis of individual-participant data from 140 000 men and women. *PLoS One* 2012; **7:** e40101.

41 Virtanen M, Ferrie JE, Singh-Manoux A, et al. Overtime work and incident coronary heart disease: the Whitehall II prospective cohort study. *Eur Heart J* 2010; **31:** 1737–44.

42 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0: The Cochrane Collaboration. Chichester: John Wiley & Sons, 2011.

43 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Chichester: John Wiley & Sons, 2008.

44 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283:** 2008–12.

45 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.

46 Egger M, Smith GD, Sterne JA. Uses and abuses of meta-analysis. *Clin Med* 2001; **1:** 478–84.

47 Holtermann A, Mortensen OS, Burr H, Søgaard K, Gyntelberg F, Suadicani P. Long work hours and physical fitness: 30-year risk of ischaemic heart disease and all-cause mortality among middle-aged Caucasian men. *Heart* 2010; **96:** 1638–44.

48 Toker S, Melamed S, Berliner S, Zeltser D, Shapira I. Burnout and risk of coronary heart disease: a prospective study of 8838 employees. *Psychosom Med* 2012; **74:** 840–47.

49 Netterstrøm B, Kristensen TS, Jensen G, Schnor P. Is the demand-control model still a usefull tool to assess work-related psychosocial risk for ischemic heart disease? Results from 14 year follow up in the Copenhagen City Heart study. *Int J Occup Med Environ Health* 2010; **23:** 217–24.

50 Tarumi K, Hagihara A, Morimoto K. A prospective observation of onsets of health defects associated with working hours. *Ind Health* 2003; **41:** 101–08.

51 Uchiyama S, Kurasawa T, Sekizawa T, Nakatsuka H. Job strain and risk of cardiovascular events in treated hypertensive Japanese workers: hypertension follow-up group study. *J Occup Health* 2005; **47:** 102–11.

52 Uchiyama S, Kurasawa T, Sekizawa T, Nakatsuka H. Risk factors of cerebro-cardiovascular events in treated hypertensive male workers in the fifth decade. *Sangyo Igaku* 1992; **34:** 318–25.

53 Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90:** 583–612.

54 Steptoe A, Kivimäki M. Stress and cardiovascular disease: an update on current knowledge. *Annu Rev Public Health* 2013; **34:** 337–54.

55 Sherman DL. Exercise and endothelial function. *Coron Artery Dis* 2000; **11:** 117–22.

56 Hamer M, Sabia S, Batty GD, et al. Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. *Circulation* 2012; **126:** 928–33.

57 Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. *Stroke* 2003; **34:** 2475–81.

58 Wendel-Vos GC, Schuit AJ, Feskens EJ, et al. Physical activity and stroke. A meta-analysis of observational data. *Int J Epidemiol* 2004; **33:** 787–98.

59 Gill JS, Zezulka AV, Shipley MJ, Gill SK, Beevers DG. Stroke and alcohol consumption. *N Engl J Med* 1986; **315:** 1041–46.

60 Mazzaglia G, Britton AR, Altmann DR, Chenet L. Exploring the relationship between alcohol consumption and non-fatal or fatal stroke: a systematic review. *Addiction* 2001; **96:** 1743–56.

61 Meschia JF, Bushnell C, Boden-Albala B, et al, and the American Heart Association Stroke Council, and the Council on Cardiovascular and Stroke Nursing, and the Council on Clinical Cardiology, and the Council on Functional Genomics and Translational Biology, and the Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; **45:** 3754–832.

62 Virtanen M, Jokela M, Nyberg ST, et al. Long working hours and alcohol use: systematic review and meta-analysis of published studies and unpublished individual participant data. *BMJ* 2015; **350:** g7772.

63 Fukuoka Y, Takeshima M, Ishii N, et al. An initial analysis: working hours and delay in seeking care during acute coronary events. *Am J Emerg Med* 2010; **28:** 734–40.